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The Structure–Activity Relationships of the Triketone Class of HPPD Herbicides†

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Abstract: The 2-benzoylcyclohexane-1,3-diones, the triketones, are a novel class of bleaching herbicides whose mode of action is the inhibition of the enzyme *p*-hydroxyphenylpyruvate dioxygenase. The structure–activity relationships of this chemical class are elucidated. An *ortho*-substituent on the aryl ring is an absolute requirement for herbicidal activity. Beyond that, the herbicidal activity of these compounds is best correlated with the overall electron deficiency of the benzoyl group induced by 2,4-disubstitution of the aryl ring, with the most electron-deficient analogs being the most active. Moreover, the degree of electron deficiency of the benzoyl group is outwardly manifested in the acidity of the molecule. The activity of these compounds is further enhanced through additional aromatic substitution in the 3-position of the aryl ring. The greater activity of these 2,3,4-trisubstituted aryl analogs over the 2,4-disubstituted aryl analogs is due to increased intrinsic activity. © 1998 Society of Chemical Industry

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Key words: benzoylcyclohexanediones; triketone; *p*-hydroxyphenylpyruvate dioxygenase; structure–activity relationships

1 INTRODUCTION

Targeting the inhibition of *p*-hydroxyphenylpyruvate dioxygenase (HPPD) as a herbicidal mode of action (MOA) is a recent, exciting development in the pesticide industry. Most, if not all, the major agrochemical companies now have or have had research projects in this area.[1–17] Discovery of HPPD as an unique and viable herbicide target was first made by Zeneca Agrochemicals in 1982 as part of an investigation of herbicidal 2-benzoyl-1,3-cyclohexanediones, referred to as the triketones.[18] Elucidation of the unique site of action of these compounds was first made in mammalian systems.[19,20] The HPPD site of action was then subsequently confirmed in plants,[21–25] and a minimum substructure hypothesis for the inhibition of HPPD was also developed.[20,26] The commercial compound sulcotrione, a post-emergent broad-leaf herbicide for use in maize in Europe, eventually resulted from these efforts, along with the development compound ZA1296 for the pre- and post-emergent broad-leaf maize market in the USA. An additional unexpected benefit from this research was the discovery of the pharmaceutical use of these triketones for the treatment of tyrosinaemia, a disorder involving increased concentrations of tyrosine in the blood, with enhanced urinary excretion of tyrosine and tyrosine-related compounds.[27] This paper will

* To whom correspondence should be addressed.
† One of a collection of papers on various aspects of agrochemicals research contributed by staff and collaborators of Zeneca Agrochemicals UK and Zeneca Ag Products USA. The papers were collected and collated by Dr B. C. Baldwin and Dr D. Tapolczay.

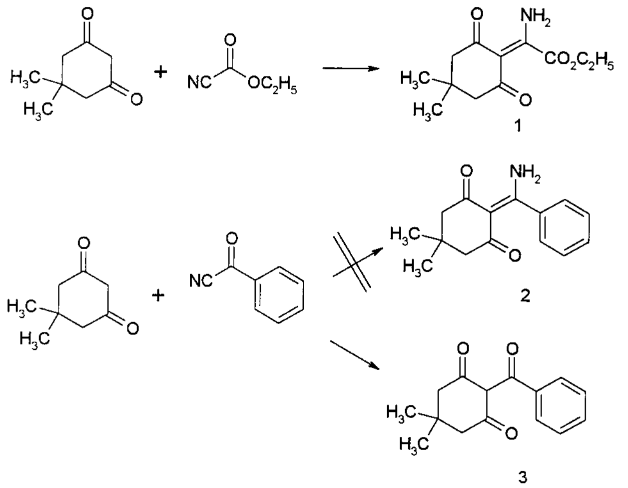


Fig. 1. Attempted preparation of sethoxydim analogs that led to triketones.

detail our work in the discovery and elucidation of the structure–activity relationships of the triketone class of HPPD herbicides.

2 BACKGROUND AND DISCOVERY

Like many other major discoveries, the discovery of the triketones was entirely serendipitous while following a rationale for the synthesis of what would be the 'breakthrough' molecule for an entirely different purpose. Their genesis started with attempts to prepare new inhibitors of acetyl-CoA carboxylase chemically patterned after sethoxydim. In particular, we were attempting to prepare other potential functional mimics of the oximino moiety of sethoxydim. The first target compound (**1**), which was prepared as shown in Fig. 1, had encouraging herbicidal activity. In an attempt to prepare phenyl analogs using the same reaction procedure, the 2-benzoylcyclohexane-1,3-dione **3** was obtained instead of the expected product **2**. Compound **3** was herbicidally inactive. As such, further interest in this class of compounds would normally have terminated. However, at that time we had an ongoing program to screen for antidotes for soya injury produced by thiocarbamate herbicides, and compound **3** was found to have antidote properties. Therefore, an analog synthesis program was initiated to optimize this antidoting effect. As part of this effort, the *ortho*-chloro analog **4** (Fig. 2) was prepared. It was found to be quite herbicidally

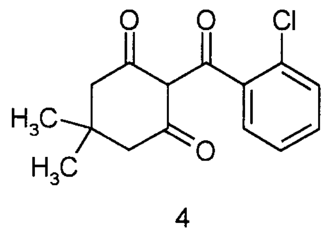


Fig. 2. First herbicidally active triketone prepared.

active with unique bleaching symptoms, and the discovery of the triketone herbicides had been made.

3 MATERIALS AND METHODS

3.1 Synthesis of test compounds

All compounds discussed in this paper were synthesized by methods previously published.[18] The structural assignments of these compounds were based on their IR, mass and [^{1}H]NMR spectra.

3.2 Biological activity

3.2.1 Pre-emergence herbicidal evaluation

On the day preceding treatment, seeds of several different weed species were planted in sandy loam soil containing only trace organic matter. Propagules were sown in individual rows using one species per row across the width of an aluminum flat. Seeding depths ranged from 1·0 to 1·5 cm and plant densities ranged from three to 25 per row depending on individual plant species.

The grass weeds planted were broadleaf signalgrass (*Brachiaria platyphylla* Nash) (BRAPP); large crabgrass (*Digitaria sanguinalis* Sap.) (DIGSA); barnyardgrass (*Echinochloa crus-galli* (L.) Beauv.) (ECHCG); rigid ryegrass (*Lolium rigidum* (Gaud) (LOLRI); fall panicum (*Panicum dichotomiflorum* Michx.) (PANDI); giant foxtail (*Setaria faberi* Horrm.) (SETFA); greef foxtail (*Setaria viridis* Beauv.) (SETVI); blackgrass (*Alopecurus myosuroides* Huds.) (ALOMY); wild oat (*Avena fatua* L.) (AVEFA) and Johnsongrass (*Sorghum halepense* Pers.) (SORHA).

The broad-leaf weeds planted were velvetleaf (*Abutilon theophrasti* (L.) Medic.) (ABUTH); redroot pigweed (*Amaranthus retrofluxus* L.) (AMARE); common lambsquarters (*Chenopodium album* L.) (CHEAL); ivyleaf morningglory (*Ipomoea hederacea* Jacq.) (IPOHE); common purslane (*Portulaca oleracea* L.) (POROL); common cockleburr (*Xanthium strumarium* L.) (XANST); and cleavers (*Galium aperine* L.) (GALAP). Additionally, yellow nutsedge (*Cyperus esculentus* L.) (CYPES) nutlets were also sown. The soil surface of the plant flats was dosed with test formulation one day after seeding. There was no pregermination.

Solutions of the test compounds were prepared by dissolving in deionised water + acetone (1 + 1 by volume) containing Tween 20® emulsifier (5 g litre^{-1}) the amounts required to provide an application rates of 50–4000 g ha^{-1}. The soil surface was sprayed inside an enclosed linear spray table with the nozzle set above the soil line. The spray table was calibrated to deliver 400 litre ha^{-1} with the application rate being between 50 and 4000 g ha^{-1}. After treatment, the flats were placed

in a greenhouse and watered as needed. The greenhouse environmental systems provided the plants with natural and artificial lighting to attain 14 h of light per day. The species AMARE, BRAPP, DIGSA, ECHCG LOLRI, PANDI, SETFA, SETVI, SORHA, ABUTH, CHEAL, IPOHE, POROL, XANST, and CYPES were maintained at 29° day and 21°C night temperatures. The species ALOMY, CHEAL, AVEFA and GALAP were maintained at 19° day and 13°C night temperatures.

The degree of weed control was evaluated and recorded 17–21 days after treatment as a percentage of weed control, i.e. the total injury to the plants due to all factors including inhibited emergence, stunting, malformation, chlorosis and other types of plant injury, as compared to the growth of the same species of the same age in an untreated control flat. The control ratings were on a scale from 0 to 100%, where 0 represented no effect, with growth equal to the untreated control and where 100 represented complete kill.

3.3 Substituent parameters and QSAR method

The physicochemical parameters of the *p*-substituent and the biological activities for the 2-[2-chloro-4-substituted benzoyl]-1,3-cyclohexanediones and the 2-[2-nitro-4-substituted benzoyl]-1,3-cyclohexanediones are summarized in Tables 1 and 2 respectively.

4 RESULTS AND DISCUSSION

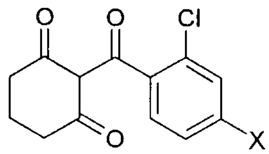
4.1 Structure–activity relationships of the phenyl ring

4.1.1 Effects of ring substitution patterns

Following the discovery of the absolute requirement of an *ortho*-substituent on the phenyl ring for herbicidal

TABLE 1

Physicochemical Parameters of *p*-Substituent and Biological Activities for 2-[2-Chloro-4-substituted benzoyl]-1,3-cyclohexanediones

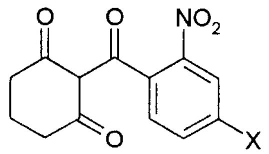


Compound	*X*	σ_p	π	*MR*	LD_{50} [a] $(g\ ha^{-1})$	*Log* LD_{50}
3	OCH_3	−0·27	−0·02	7·87	5100	3·71
4	CH_3	−0·17	0·56	5·65	2800	3·45
5	H	0	0	1·03	830	2·92
6	F	0·06	0·14	0·92	1600	3·2
7	Cl	0·23	0·71	6·03	180	2·26
8	NO_2	0·78	−0·28	7·36	550	2·74
9	SO_2CH_3	0·72	−1·63	13·49	72	1·86

[a] Dose required to obtain an average weed control rating of 50% on seven different broad-leaf weed species.

TABLE 2

Physicochemical Parameters of *p*-Substituent and Biological Activities for 2-[2-Nitro-4-substituted benzoyl]-1,3-cyclohexanediones



Compound	*X*	σ_p	π	*MR*	LD_{50} [a] $(g\ ha^{-1})$	*Log* LD_{50}
10	H	0	0	1·03	810	2·91
11	Cl	0·23	0·71	6·03	42	1·62
12	CF_3	0·54	0·88	5·02	14	1·16
13	SO_2CH_3	0·72	−1·63	13·49	13	1·12

[a] Dose required to obtain an average weed control rating of 50% on seven different broad-leaf weed species.

activity, attention was focused on determining what additional phenyl substitutions were allowable. To accomplish this structure-space examination, a series of 2,X-dichloro- and 2,X,Y-trichlorophenyl analogs were prepared. We found the 2,4-disubstitution and the 2,3,4-trisubstitution pattern to be the most active, with the 2,4,5-trisubstitution the least active. The relative rankings of the other isomers are as shown in Fig. 3.

4.1.2 Electronic effects of phenyl substituents on activity

To ascertain the electronic effects of the phenyl substituents on activity, if any, a series of 2-chloro-4-X-phenyl analogs was prepared wherein the 4-substituent varied from electron-donating to electron-withdrawing. Some of the compounds prepared, together with their herbicidal activities (expressed as the average LD_{50} for control of seven different broad-leaf weed species in pre-emergent applications) are shown in Table 1. Linear regression analyses were conducted, looking for any correlation with either Hammett sigma(σ_P), molar refractivity (MR), or log P (π) of the p-substituent. No correlations were immediately apparent. This was not completely unexpected, since there are numerous factors such as soil adsorption, cuticle penetration, root uptake and phloem mobility which contribute to herbicidal activity in addition to affinity for the HPPD enzyme. It seemed unlikely that these factors would be convergently/similarly affected by one or two physicochemical properties of the molecule. However, we observed a trend correlating increasing pre-emergent herbicidal efficacy on broad-leaf weeds with higher sigma values if the nitro analog was removed from consideration (Fig. 4). Given the known susceptibility of nitro groups to reduction *in vivo* in plants and soil, it was decided to determine if this trendline was valid by preparing another analog with a p-substituent whose sigma value was comparable to that of nitro but which was metabolically more stable. The methylsulfonyl group ($\sigma = 0{\cdot}72$) was chosen as this replacement for the nitro group ($\sigma = 0{\cdot}78$). To our great satisfaction, the methylsulfonyl analog was indeed as active as expected with the earlier trendline prediction. A graph of the log LD_{50} versus sigma of the p-substituent with the methylsulfonyl analog now replacing the nitro analog is shown in Fig. 5.

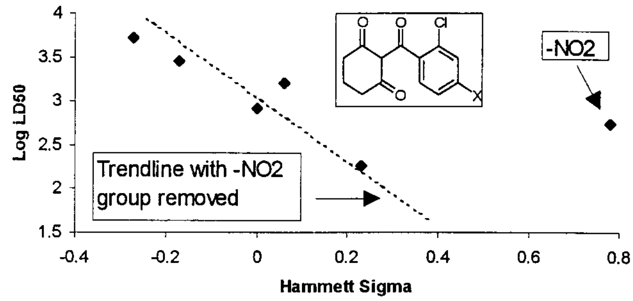


Fig. 4. Log LD_{50} versus Hammett sigma of p-substituent.

This correlation was a major revelation in the development of triketone herbicides since it suggested that even more active compounds could be obtained using even more electron-withdrawing substituents and a massive research effort on these compounds was initiated at the Western Research Center. In particular, efforts expanded into the synthesis of *ortho*-substituted phenyl analogs other than chloro. One major sub-class of active analogs that resulted from this effort was the *ortho*-nitro analogs. Unlike the herbicidally inactive *para*-nitro analog mentioned above, these *ortho*-nitro analogs were active, presumably due to their greater metabolic stability. Given the initial success in correlating activity with the Hammett sigma or electron-withdrawing capability of the p-substituent of o-chlorophenyl analogs, it was important to determine if this correlation would hold true for *ortho*-substituted analogs other than chloro. Therefore, a similar analysis was conducted on the group of o-nitrophenyl analogs as shown in Table 2. A similar trendline does exist, as shown in Fig. 6, the graph of LD_{50} versus Hammett sigma constants.

Given that there is strong correlation between activity and the electron-withdrawing capability of the *para*-substituent, attention then turned to the analysis of the possible additional electronic effects of the *ortho*-substituent on activity. This was of particular interest to

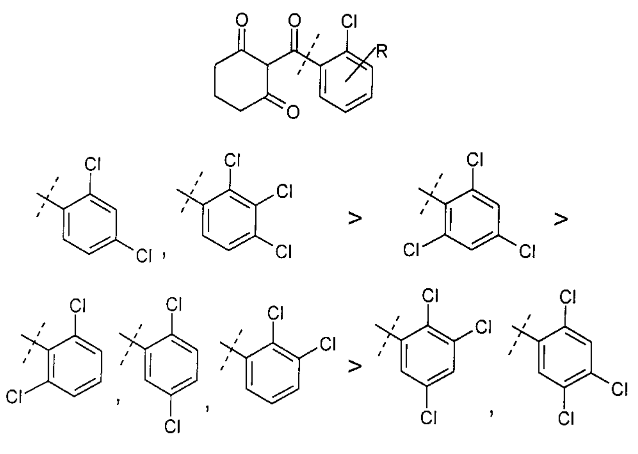


Fig. 3. Relative herbicidal activity of di- and trichlorobenzoyl analogs.

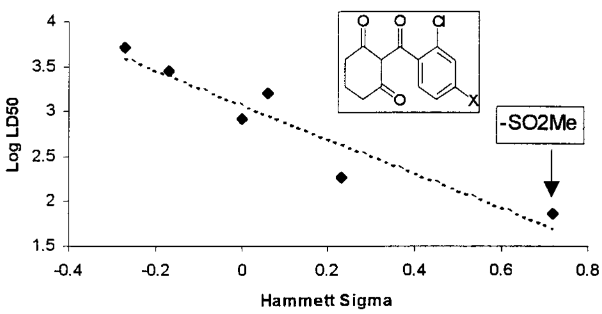


Fig. 5. Log LD_{50} versus Hammett sigma of p-substituent.

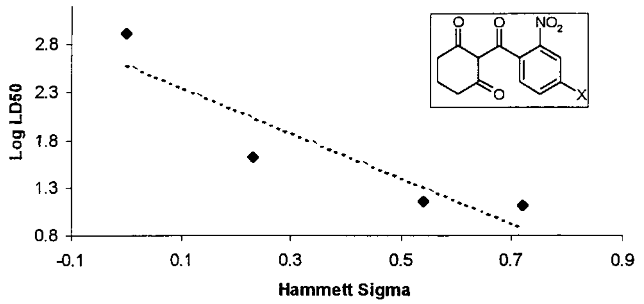


Fig. 6. Log LD_{50} versus Hammett sigma of *p*-substituent of *o*-nitro triketones.

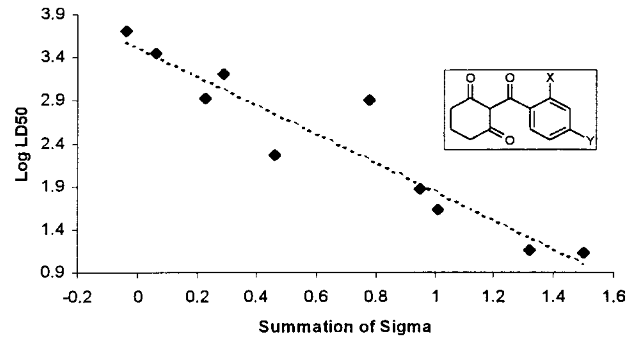


Fig. 7. Log LD_{50} versus summation of Hammett sigma of *ortho* and *para*-substituents.

us since we found the *ortho*-nitro analogs to be consistently more active than their corresponding *ortho*-chloro analogs. Given that the nitro group is more electron-withdrawing than the chloro group, we wondered if the activity could simply be correlated with the sum of the Hammett sigma values for the *ortho*- and *para*-substituents (Table 3). A graph of the sum of Hammett sigma values of the *ortho*- and *para*-substituents versus log LD_{50} against broad-leaf weeds in pre-emergent applications was made (Fig. 7). The sigma values that were used for this analysis were the σ_p values for the substituent regardless of its position, no corrections being made for *ortho*-effects. As shown in Fig. 7, there is a strong correlation between herbicidal activity and the overall electron density of the phenyl ring, the most active analogs being those with the most electron-deficient rings and the least active those with the most electron-rich rings.

Since the phenyl ring is in direct conjugation with the triketone system, it became quite obvious at this juncture that this correlation between activity and electron deficiency of the phenyl ring may simply be a result of the acidity of the molecule. The enol tautomers of the 2-benzoyl-1,3-cyclohexanedione system can be viewed as vinylogous benzoic acids (Fig. 8). As such, 2-(2-nitrobenzoyl)- 1,3-cyclohexanedione should be more acidic than 2-(2-chlorobenzoyl)- 1,3-cyclohexanedione.

To ascertain if this was correct, the pK_a values for a series of analogs were measured. The data are shown in Table 3, and a graph of pK_a versus activity (Fig. 9) is consistent with our hypothesis that herbicidal activity is correlated with the acidity of the molecule.

A similar analysis of the effect of the *meta*-substituent on activity was attempted but was found not to be as straightforward. This analysis was complicated by the propensity of some of the compounds to undergo an

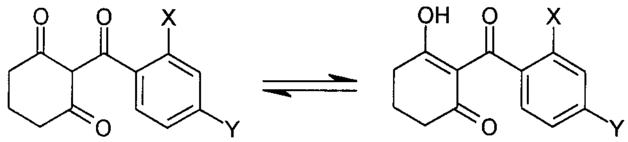
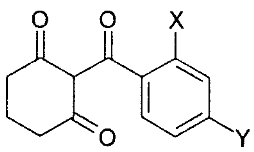


Fig. 8. Enol tautomer of triketones.

TABLE 3

Biological Activities and Summation of σ_p Values of the *o,p*-Substituents of 2-[2,4-Disubstituted benzoyl]-1, 3-cyclohexanediones



Compound	*X*	*Y*	*σ_p of X*	*σ_p of Y*	*$\Sigma\sigma$*	*LD_{50} [a]($g\ ha^{-1}$)*	*Log LD_{50}*	*pK_a*
3	Cl	OCH_3	0·23	−0·27	−0·04	5100	3·71	4·09
4	Cl	CH_3	0·23	−0·17	0·06	2800	3·45	3·83
5	Cl	H	0·23	0	0·23	830	2·92	3·81
6	Cl	F	0·23	0·06	0·29	1600	3·2	3·77
7	Cl	Cl	0·23	0·23	0·46	180	2·26	3·5
9	Cl	SO_2CH_3	0·23	0·72	0·95	72	1·86	3·2
10	NO_2	H	0·78	0	0·78	810	2·91	3·6
11	NO_2	Cl	0·78	0·23	1·01	42	1·62	3·44
12	NO_2	CF_3	0·78	0·54	1·32	14	1·16	3·1
13	NO_2	SO_2CH_3	0·78	0·72	1·5	13	1·12	3·04

[a] Dose required to obtain an average weed control rating of 50% on seven different broad-leaf weed species.

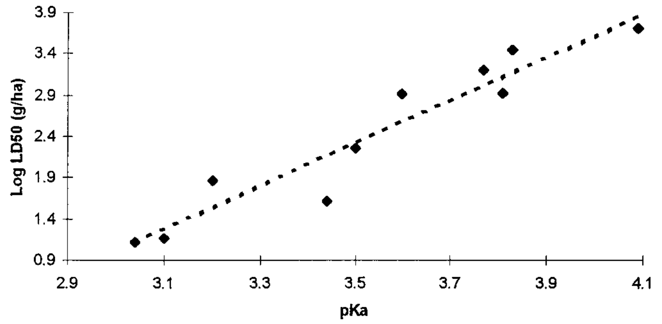


Fig. 9. Log herbicidal activity versus pKa of triketone molecule.

intramolecular cyclization to a dihydroxanthenone (Fig. 10). This cyclization presumably occurs via displacement of those *ortho*-substituents which are capable of being a leaving group, e.g. halogen, nitro, and alkanesulfonyl, by the enol tautomer of the tricarbonyl moiety. Moreover, it occurs most readily when the *meta*-substituent is electron-withdrawing, as such substituents activate the *ortho*-position towards nucleophilic attack. Based upon these findings, we reasoned that a *meta*-substituent such as alkoxy, which is resonantly electron-donating at its *ortho*-positions, thereby hindering dihydroxanthenone formation, but inductively electron-withdrawing to the carbonyl system, thus increasing acidity, would be ideal. Indeed, in support of our rationale, the 2-chloro-3-alkoxy-4 -alkanesulfonylbenzoyl compounds were found to be significantly more active than their 2-chloro-4- alkanesulfonylbenzoyl analogs. The validity of this explanation for the potentiating effects of a *meta*-alkoxy group was significantly compromised when similar potentiating effects were obtained for 2-methyl-3-alkoxy- 4-alkylsufonylbenzoyl analogs. For these compounds, dihydroxanthenone formation is not possible, as the 2-methyl group is not a leaving group. Additionally, it was found that the length of the *meta*-alkoxy group had a dramatic effect on the weed spectrum (*vide infra*). These two findings now lead us to believe that the potentiating effect of a *meta*-alkoxy group is not due to any electronic effects with the phenyl ring but rather to some secondary binding with the receptor at the active site itself (*vide infra*).

4.1.3 Size limitations of phenyl ring substituents

Size limitations for the *ortho*, *meta*, and *para*-positions of the phenyl ring were determined by comparing the activity of a homologous series of compounds where the substituents in the other phenyl positions were kept constant. In particular, the methyl, ethyl, propyl, isopropyl and butyl homologs of alkoxy, alkylthio and alkylsulfonyl substituents were used extensively as the probes. For both the *ortho-* and the *para*-positions, it was found that the methyl analogs were generally more active than their higher homolog counterparts. In some cases, the activity of the methyl and ethyl analogs were similar, but the drop-off in activity was always quite evident by the propyl analog. The situation for the *meta*-position, especially for alkoxy substitution, was quite different. A significant and progressive increase in the level of activity on grass weed species was observed as the alkoxy group was lengthened from methoxy to butoxy. Substituted alkoxy groups such as ethoxyethoxy also had comparable effects in altering the weed spectrum. Thus, it appears that there is a pocket for the *meta*-substituent that is more accommodating than for either the *ortho-* or the *para*-substituent. Additionally, given the drastic effects observed on the weed spectrum, it is speculated that there can be significant secondary binding interactions associated with the *meta*-substituent as well. This hypothesis was supported by subsequent intrinsic binding assays against the maize HPPD enzyme. For example, whereas sulcotrione, 2-(2-chloro-4-methylsulfonyl-benzoyl)-1,3-cyclohexanedione, has an IC_{50} of 50 nM, the corresponding analog with an additional 3-ethoxy group on the phenyl ring, 2-(2-chloro-3-ethoxy-4-methylsulfonylbenzoyl)-1,3-cyclohexanedione, has an IC_{50} of 2 nM.

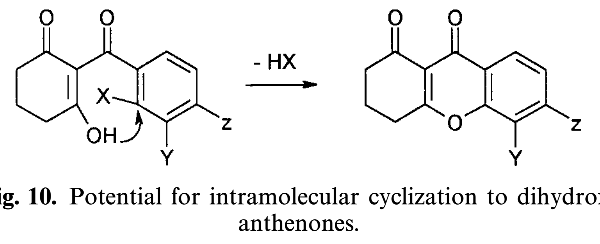


Fig. 10. Potential for intramolecular cyclization to dihydroxanthenones.

4.2 Mode of action

As can be expected with any new mode of action, the elucidation of the site of action of the triketones was not straightforward. Initial publications revealed that in-vivo levels of phytoene were elevated in treated plants. This led the investigators to conclude that the mode of action of these compounds might possibly be the inhibition of the desaturation reactions of carotenoid biosynthesis.[28,29] Later work, however, revealed that the triketones do not inhibit phytoene desaturase *in vitro*.[30] This led these investigators to postulate that the triketones require metabolic modification before becoming active.[30] Our first clue to the unique mode of action of the triketone herbicides was the discovery that rats treated with these compounds became tyrosinemic.[19,20] This finding then soon led to the identification of *p*-hydroxyphenylpyruvate dioxygenase (HPPD) as the site of inhibition in mammals.[19] Confirmation of this site of action in plants was first accomplished by measuring the tyrosine and plastoquinone levels in treated plants. In plants, HPPD is a component of the biosynthetic pathway to plastoquinone (Fig. 11). As such, inhibition of HPPD leads to increased tyrosine levels and to the depletion of plastoquinone.[21] Blea-

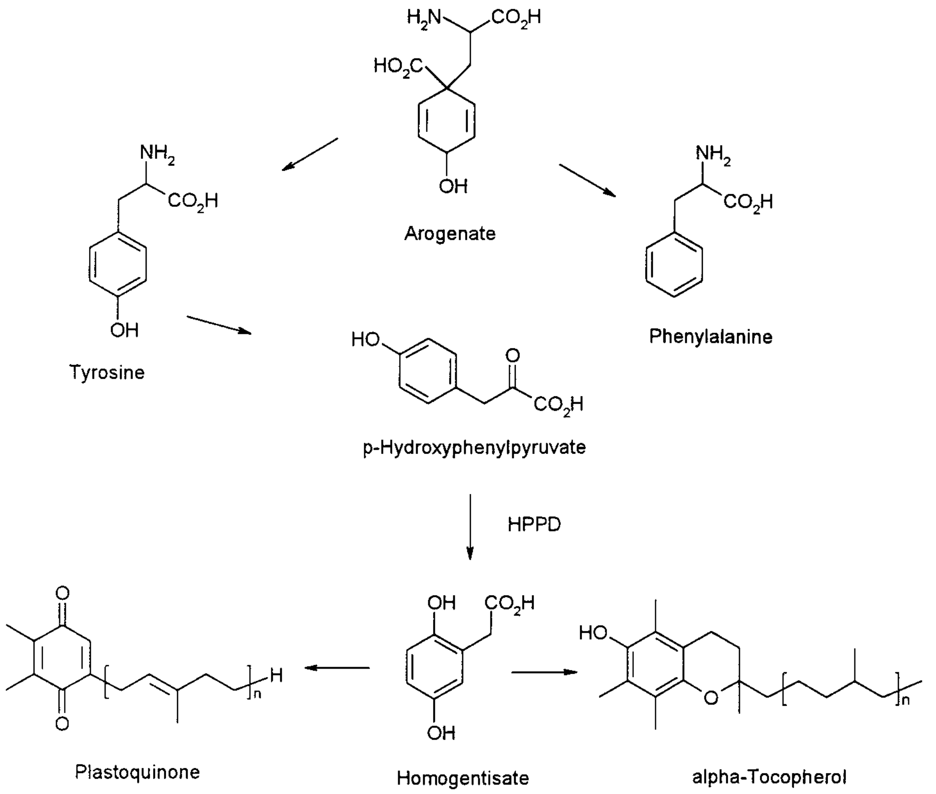


Fig. 11. Plastoquinone biosynthetic pathway.

ching symptoms result because the latter is a critical cofactor for phytoene desaturase.[31–33] Its depletion results in the reduction of carotenoids leading to bleaching symptoms. Plant HPPD was subsequently found to be inhibited by the triketones.[21,23–25]

5 CONCLUSIONS

The herbicidal activity of the 2-benzoyl-1,3-cyclohexanedione class of HPPD compounds is acutely affected by the substituents on the phenyl ring. The substituents affect both the acidity of the molecule, which is presumably important for transport, as well as binding affinity to the HPPD enzyme.

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REFERENCES

1. Fischer, R., Bretschneider, T., Santel, H., Luerssen, K., Schmidt, R. R. & Erdelen, C. (Assignee: Bayer AG), New substituted 3-benzoylpyrrolidine-2,4-dione derivatives useful for insecticides, acaricides, nematocides, weedkillers, etc. DE 4223015, 1992.
2. Plath, P., Westphalen, K., Gerber, M. & Walter, H. (Assignee: BASF AG), Herbicidal saccharin carboxylic acid derivatives and method for their preparation. WO 96/05184, 1996.
3. Brunner, H. (Assignee: Ciba-Geigy AG). New Herbicide. EP 353 187, 1989.
4. Tseng, C. (Assignee: Dupont), Herbicidal ketals and spirocycles. WO 97/01550, 1997.
5. Inayoshi, Y., Yamasaki, M. & Aizawa, S. (Assignee: Hodogaya Chemical Co.). Preparation of iminobenzyl derivatives as herbicides. JP 02 03 649, 1990.
6. Stark, H., Bauer, K. & Bieringer, H. (Assignee: Hoechst AG), Haloalkoxy-substituted benzoylcyclohexanedione as herbicide and plant growth regulator. EP 0 502 492, 1992.
7. Muller, S., Schutze, R., Bauer, K. & Bieringer, H. (Assignee: Hoechst Schering Agrevo), Benzoylcyclohexenones, methods of preparing them and their use as herbicides and plant growth regulators. WO 94/13619, 1994.
8. Morita, T., Oono, T., Shimozono, T., Hirayama, K., Ishikawa, H., Yoshizawa, H. & Takeuchi, T. (Assignee: Hokko Chem Ind Co.), Cyclohexanediones and herbicides containing them. JP 06,247,891, 1994.
9. Shibata, M., Nasuno, I., Koike, K., Sakamoto, M. & Takashima, Y. (Assigness: Idemitsu Kosan), New (pyrazolylcarbonyl)benzothiane dioxide derivatives useful as selective herbicide for paddy rice and corn, highly active against weeds. WO 95/13275, 1995.
10. Geach, N. J., Gilmour, J., Hatton, L. R. & Smith, P. H. G. (Assignee: May and Baker), Cyclic diones. EP 0 278 742, 1988.
11. Adachi, H., Tanaka, K., Kawana, T. & Hosaka, H. (Assignee: Nippon Soda), Herbicidal 3-

substitutedbenzoyl-bicyclo[4,1,0]heptane-2,4-dione derivatives. US Patent 5 294 598, 1994.

12. Watanabe, J., Kondo, Y., Hatanaka, M., Ikai, T., Suzuki, K., Nawamaki, T. & Watanabe, S. (Assignee: Nissan Chemical Industries), Substituted benzoyl derivatives and herbicidal compositions. US Patent 5 145 502, 1992.
13. Cramp, S. M., Musil, T., Pettit, S. N. & Smith, P. H. G. (Assignee: Rhône Poulènc), 4-Benzoyl isoxazoles and their use as herbicides. EP 0 609 797, 1994.
14. Ashmore, J. W. (Assignee: Rohm and Haas), Herbicidally active enols. US Patent 4 781 750, 1988.
15. Lee, S. (Assignee: Sandoz), Heterocyclic diones as plant growth regulators. US Patent 5 336 622, 1994.
16. Angermann, A., Franke, H., Rees, R. & Johann, G. (Assignee: Schering). Preparation of 2-(thiadiazolylcarbonyl)cyclohexan-1,3-diones as herbicides. EP 0 338 525, 1989.
17. Komatsubara, K., Sato, T., Mikami, K., Yamada, J. & Sato, M. (Assignee: SDS Biotech), Preparation of benzoylcycloalkenones as herbicides. JP 06 25 144, 1994.
18. Michaely, W. J. & Kratz, G. W., Certain 2-(2-substitutedbenzoyl)-1,3-cyclohexanediones. EP 0 135 191, 1986.
19. Ellis, M. K., Whitfield, A. C., Gowans, L. A., Auton, T. R., Provan, W. M., Lock, E. A. & Smith, L. L., Inhibition of 4-hydroxyphenylpyruvate dioxygenase by 2-(2-nitro-4-trifluoromethylbenzoyl)-cyclohexane-1,3-dione and 2-(2-chloro-4-methylsulfonylbenzoyl)-cyclohexane-1,3-dione. *Toxicol. Appl. Pharmacol.*, **133** (1995) 12–19.
20. Lee, D. L., Prisbylla, M. P., Cromartie, T. H., Dagarin, D. P., Howard, S. H., Provan, W. M., Ellis, M. K., Fraser, T. & Mutter, L. C., The discovery and structural requirements of inhibitors of *p*-hydroxyphenylpyruvate dioxygenase. *Weed Sci.*, **45** (1997) 601–9.
21. Prisbylla, M. P., Onisko, B. C., Shribbs, J. M., Adams, D. O., Liu, Y., Ellis, M. K., Hawkes, T. R. & Mutter, L. C., The novel mechanism of action of the herbicidal triketones. *Proc. Brighton Crop Prot. Conf.—Weeds*, **2** (1993) 731–8.
22. Prisbylla, M. P., Lee, D. L., Cromartie, T. H., Dagarin, D. P. & Howard, S. W., Mode of action studies on structurally related triketone HPPD inhibitors. *Inter. Chem. Congr. of Pacific Basin Soc. Book of Abstracts*, **1** (1995) 94.
23. Schultz, A., Ort, O., Beyer, P. & Kleinig, H., SC-0051, a 2-benzoylcyclohexane-1,3-dione bleaching herbicide, is a potent inhibitor of the enzyme *p*-hydroxyphenylpyruvate dioxygenase. *FEBS Lett.*, **318** (1993) 162–6.
24. Secor, J., Inhibition of barnyardgrass 4-hydroxyphenylpyruvate dioxygenase by sulcotrione. *Plant Physiol.*, **106** (1994) 1429–33.
25. Barta, I. C. & Boger, P., Benzoylcyclohexanedione herbicides are strong inhibitors of purified *p*-hydroxyphenylpyruvic acid dioxygenase of maize. *Pestic. Sci.*, **45** (1995) 286–7.
26. Lee, D. L., Mutter, L. C., Dagarin, D. P., Howard, S. W. & Fraser, T., Structure–activity relationships of HPPD herbicides: Benzoylphenols and β-diketones. *Inter. Chem. Congr. of Pacific Basin Soc. Book of Abstracts*, **1** (1995) 91.
27. Ellis, M. K., Lindestedt, S. T., Lock, E. A., Markstedt, M. E. H., Mutter, L. C. & Prisbylla, M. P., Use of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione in the treatment of tyrosinaemia and pharmaceutical compositions. WO 93/00080, 1992.
28. Mayonado, D. J., Hatzios, K. K., Orcutt, D. M. & Wilson, H. P., Evaluation of the mechanism of action of the bleaching herbicide SC-0051 by HPLC analysis. *Pestic. Biochem. Physiol.*, **35** (1989) 138–45.
29. Soeda, T. & Uchida, T., Inhibition of pigment synthesis by 1,3-dimethyl-4-(2,4-dichlorobenzoyl)-5-hydroxypyrazole, norflurazon and new herbicidal compounds in radish and flatsedge plants. *Pestic. Biochem. Physiol.*, **29** (1987) 35–42.
30. Sandman, G. & Boger, P., Atypical inhibition of phytoene desaturation by 2-(4-chloro-2-nitrobenzoyl)-5,5-dimethylcyclohexane-1,3-dione. *Pestic. Sci.*, **30** (1990) 353–5.
31. Mayer, M. P., Beyer, P. & Kleinig, H., Quinone compounds are able to replace molecular oxygen as terminal electron acceptor in phytoene desaturase in chromoplast of *Narcissus pseudonarcissus* L. *Eur. J. Biochem.*, **191** (1990) 359–63.
32. Mayer, M. P., Nievelstein, V. & Beyer, P., Purification and characterization of a NADPH-dependent oxidoreductase from chromoplast of *Narcissus pseudonarcissus*: a redox-mediator possibly involved in carotene desaturation. *Plant Physiol. Biochem.*, **30** (1992) 389–98.
33. Norris, S. R., Barrette, T. R. & DellaPenna, D., Genetic dissection of carotenoid synthesis in arapidopsis defines plastoquinone as an essential component of phytoene desaturation. *Plant Cell*, **7** (1995) 2139–49.